Combination Trial: Goals

- Determine the highest non toxic combination
- Evaluate synergy at optimal dosage and in dose response
- Determine combination toxicity index and host recovery time

Combination Trial: Design

Three arms dose response study

- Use 3 to 4 groups for each single agents
- Use 6 to 10 groups for the combination

Top dosage should be selected to produce an LD20 or greater.

- Tumors and drug should be injected by different routes
- For each agent, select optimal schedule and optimal route
- Same total treatment duration

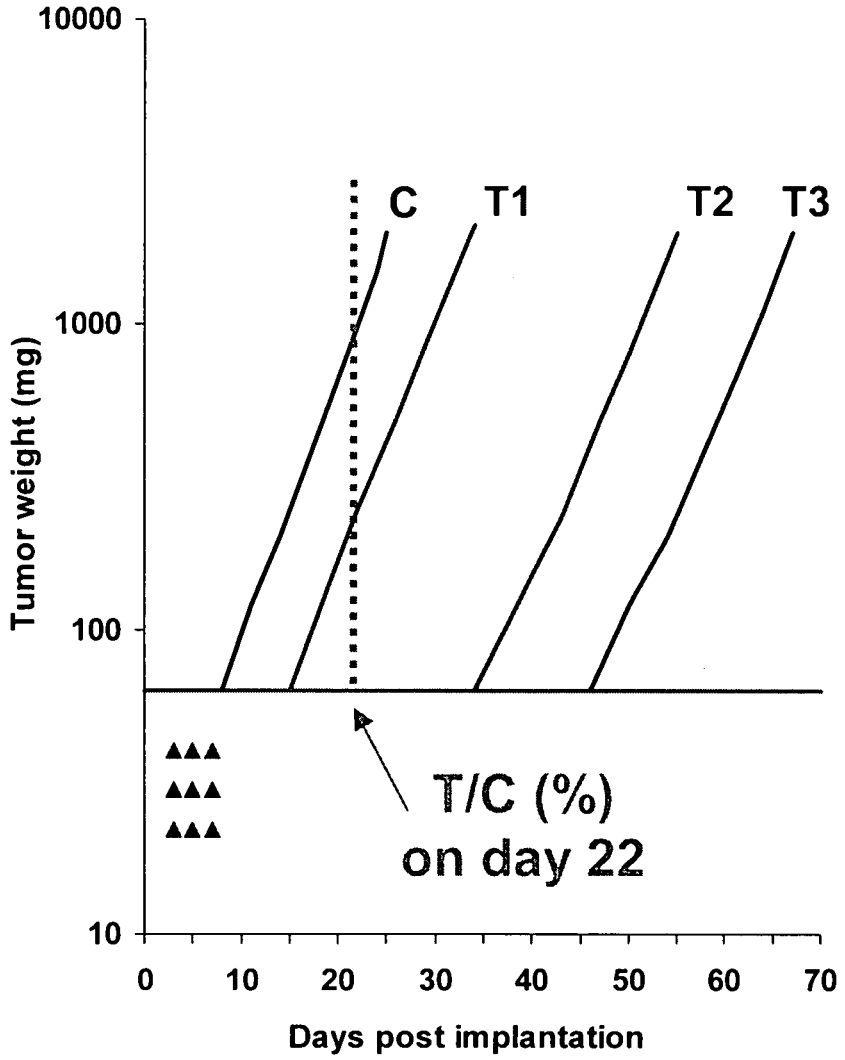
EFFICACY END POINTS (I)

Early stage sc tumor

Tumor growth inhibition

T/C (%) = median tumor weight of treated group (T) / median tumor weight of control group (C) x 100

T/C > 42 %: inactive, T/C < 10 %: high antitumor activity



Efficacy End Points (II)

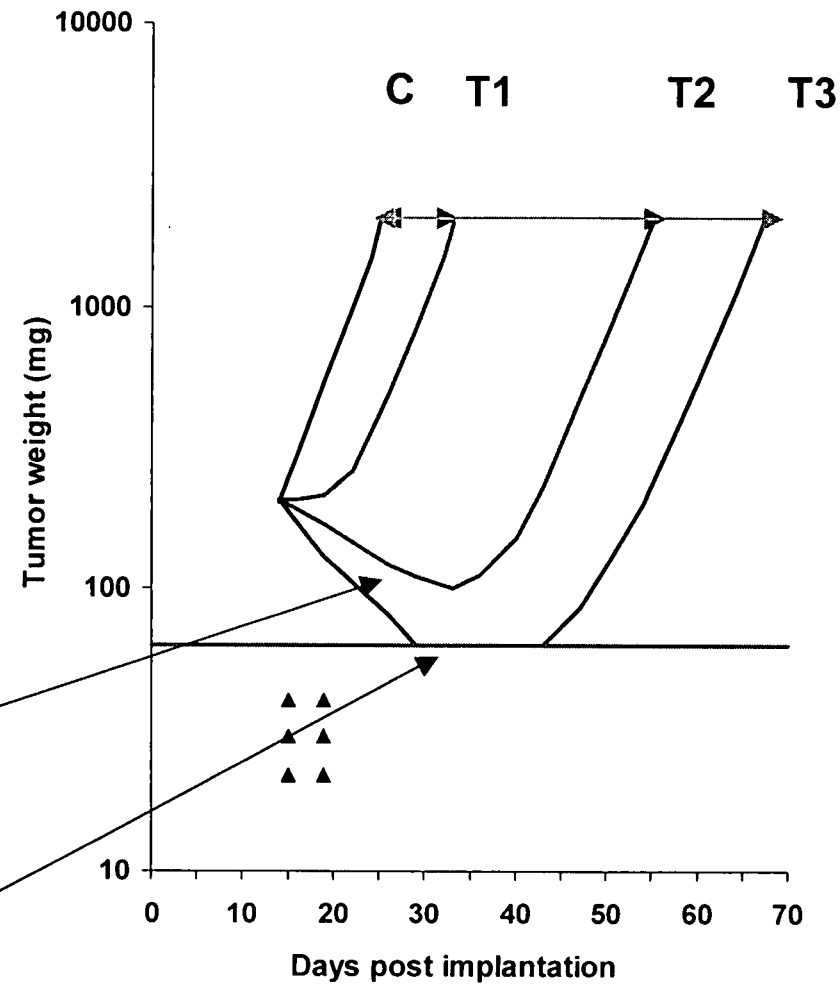
Advanced sc tumor

Tumor growth delay (T-C) in days: Median time for treated (T) versus control (C) tumor groups to reach a predetermined size.

Log cell kill: (T-C) / [3.32 x (tumor doubling time)]
lck < 0.7: inactive,
lck greater than or equal 0.7 active,
lck > 2.8: highly active

Response rate:

PR partial regression (≥ 50%)
CR complete regression (below limit of palpation)



Combination – End Points

THERAPEUTIC SYNERGY : if the combination is more active than either agent used alone at the highest non toxic dose

- (≥1 log above the target log cell kill)

Combination – End Points

- POSSIBLE OUTCOMES: No way to know a priori the combination result
- (1) Activity and Synergism
- (2) Activity and No Synergism
- (3) Antagonism in Activity
- (4) Antagonism and no activity
- Results 1 and 2 are desirable. Results 3 and 4 are undesirable.

POSSIBLE OUTCOMES

- No way to know a priori the combination result
- Thus, one could not have reasonably expected from the prior art the result of cyclopropyl taxane and another anti-cancer agent.
- Practical experiences prove that point
- Note from those experiences:
- With 5-FU, taxotere did better in combination, but with doxo, cyclopropyltaxane did better.